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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,769	09/05/2003	Brian Varnum	01-1554-F	8860

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EXAMINER	
SKELDING, ZACHARY S	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/656,769	VARNUM ET AL.	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-49,52,53 and 55-61* is/are pending in the application.

4a) Of the above claim(s) *3,4,6-9,12-31,39,41,43,45,60 and 61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,11,32-38,40,42,44,46-49,52,53,55,56 and 59* is/are rejected.

7)☒ Claim(s) *5,10,57 and 58* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *April 14, 2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed April 14, 2006 has been entered.

   Claims 11, 49, 52, 53, 56 and 59 have been amended.
   Claims 50, 51 and 54 are canceled.

   Claims 1-49, 52, 53, and 55-61 are pending.

   Claims 1, 2, 5, 10, 11, 32-38, 40, 42, 44, 46-49, 52, 53 and 55-59 are under consideration in the instant application as they read on the elected invention of Group III, an antibody that binds IL-1R1 comprising SEQ ID NOs: 16, 18, 63, 66, 69, 71, 73 and 75.

   Claims 3, 4, 6-9, 12-31, 39, 41, 43, 45, 60 and 61 have been withdrawn as being drawn to a non-elected invention.

2. The rejections of record can be found in the previous Office Action, mailed October 11, 2005.

   This Office Action is in response to Applicant's amendment filed April 14, 2006.

   The text of those sections of Title 35 U.S.C. not included in this Office Action can be found in a prior action.

3. The previous objections have been withdrawn in view of applicant's amendment to the claims.

   The previous rejection of claims 5, 10, 50, 51, 53, 54, 57 and 58 under 35 U.S.C. § 112, 1st paragraph, enablement has been withdrawn in view of applicant's arguments and amendments.

   The previous rejection of claims 5, 10, 50, 51, 53, 54, 57 and 58 under 35 U.S.C. § 112, 1st paragraph, written description has been withdrawn in view of applicant's arguments and amendments.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 2, 11, 32-38, 40, 42, 44, 46-49, 52, 53, 56 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A. "wherein the antibody inhibits binding of either IL-1β or IL-1ra to IL-1R1"

This is a **New Grounds of Rejection.**

Applicant has amended **claim 11** to include the limitation, "wherein the antibody inhibits binding of either IL-1β or IL-1ra to IL-1R1," to and pointed to example 3, page 73 for support.

As disclosed in the instant specification at page 73, 2nd paragraph, the antibody comprising SEQ ID NOs: 16 and 18 (15C4) blocks IL-1β binding to IL-1R1 but does not "significantly interfere" with IL-1ra binding.

One of skill in the art, using the assay described in example 3, could *screen* for an antibody with at least 90% identity to antibody comprising SEQ ID NOs: 16 and 18 which maintains the ability of the wild type antibody to inhibit the binding of **IL-1β to IL-1R1**.

However, one of skill in the art is **not** enabled to identify, without undue experimentation, an antibody with at least 90% identity to antibody comprising SEQ ID NOs: 16 and 18 which inhibits binding of **IL-1ra to IL-1R1** because to do so would require a *selective* procedure as the vast majority of antibodies with at least 90% identity to antibody comprising SEQ ID NOs: 16 and 18 will either continue to **not antagonize IL-1ra binding** or will cause the antibody to **not bind IL-1R1 at all**, rather than giving the antibody a ***new ability*** to inhibit the binding of IL-1ra.

Applicant is invited to amend the claim to "wherein the antibody inhibits binding of IL-1β to IL-1R1."

B. Antibodies comprising less than the complete light and heavy chain variable domains

With respect to **claims 1, 2, 32-38, 40, 42, 44, 46-49, 52 and 53**, which recite, or depend from claims which recite, antibodies comprising less than the complete light and heavy chain variable domains, applicant's arguments have been considered but are not found convincing essentially for the reasons of record set forth in the previous Office Action.

Applicant argues that "while it may be true that both heavy and light chain variable regions are necessary for antigen binding in some cases, however, single variable regions capable of antigen binding can be selected." Applicant provides multiple documents that disclose selective procedures for identifying single variable regions polypeptides that can bind antigen.

Applicant's argument is not found persuasive essentially for the reasons of record set forth in the previous Office Action, more particularly, because Janeway et al. teach that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (See Janeway et al., Immunobiology, 6th Ed., Garland Science, pp. 110-112 (2004), cited in the previous Office Action).

Applicant has not provided *objective evidence* to indicate that any of the *particular* antibody variable regions disclosed in the instant application can bind to antigen on its own, in the absence of a complementary heavy or light chain variable region containing all three CDRs. Moreover, the instant specification does not provide sufficient guidance or direction to enable one of skill in the art, without undue experimentation, to make an antibody that specifically binds IL-1R1 starting with molecules comprising **a subset** of the six CDRs required for antibody binding to antigen with a reasonable expectation of success.

Thus, in view of the lack of predictability of the art to which the invention pertains, the lack of working examples, and the level of skill and knowledge in the art, undue experimentation would be required for one of skill in the art to make the claimed antibodies.

C. Antibody that specifically binds YSV

With respect to **claims 56 and 59**, which recite an antibody that binds specifically "to the amino acid sequence YSV of IL-1R1", applicant's arguments have been considered but are not found convincing essentially for the reasons of record set forth in the previous Office Action.

Applicant argues that the instant specification "provides exemplary antibodies that bind IL-1R1 through the sequence YSV (see Examples 5 and 9)," and thus claims 56 and 59 are enabled.

Applicant's argument is not found persuasive because the claims as written, given their broadest reasonable interpretation consistent with the specification, encompass in their breadth antibodies that bind not only YSV in the context of IL-1R1 but also a YSV peptide, and therefore are not enabled for the reasons set forth in the previous Office Action, i.e., that Harlow et al. teach that six residues are the smallest synthetic peptides that elicit an antibody response and that the instants specification does not provide sufficient direction or guidance to use YSV to make an antibody.

In summary, in view of the lack of predictability of the art to which the invention pertains, the lack of working examples, and the level of skill and knowledge in the art, undue experimentation would be required to practice the claimed invention.

6. Claims 1, 2, 32-38, 40, 42, 44, 46-49, 52, 53, 56 and 59 are rejected under **35 U.S.C. § 112, 1st paragraph, written description** for the reasons of record set forth in the previous Office Action.

With respect to claims 1, 2, 32-38, 40, 42, 44, 46-49, 52 and 53, which recite or depend upon claims which recite, antibodies comprising less than the complete light and heavy chain variable domains, Applicant's arguments have been considered but are not found convincing essentially for the reasons of record set forth in the previous Office Action.

Furthermore, with respect to claims 56 and 59 which recite an antibody that binds specifically "to the amino acid sequence YSV of IL-1R1", Applicant's arguments have been considered but are not found convincing essentially for the reasons of record set forth in the previous Office Action.

Applicant argues that selective procedures for identifying single variable regions polypeptides that can bind antigen are known in art, that plural anti-IL-1R1 antibody species are described in the instant specification and the structure, function (via functional assays) and epitope specificity of the antibodies is provided.

Applicant's argument is not found persuasive because the instant specification does not indicate that any of the heavy or light chain variable regions of the *particular* anti-IL-1R1 antibody species disclosed can bind to antigen on its own, in the absence of its complementary heavy or light chain variable region. Applicants do not possess the claimed invention. The skilled artisan cannot envision all the contemplated heavy or light chain possibilities recited in the instant claims. Moreover, Applicants have not demonstrated possession of a single species of antibody that can recognize isolated YSV polypeptide.

Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

7. This is a **New Matter** rejection **New Grounds of Rejection.**

Claim 11 is rejected under **35 U.S.C. 112, first paragraph**, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant has amended claim 11 to add the limitation, "wherein the antibody inhibits binding of either IL-1β or IL-1ra to IL-1R1," and pointed to example 3, page 73 of the instant specification for support.

The specification as filed does not provide a sufficient written description of the antibody of claim 11 "wherein the antibody inhibits binding of either IL-1β or IL-1ra to IL-1R1." The specification does not provide blazemarks nor direction for the antibody of claim 11 "wherein the antibody inhibits binding of either IL-1β or IL-1ra to IL-1R1." This limitation, which was not clearly disclosed in the specification as-filed, changes the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

As disclosed in the instant specification at page 73, 2nd paragraph, the claimed antibody, which comprises SEQ ID NOs: 16 and 18 (antibody 15C4), blocks IL-1β binding to IL-1R1 but does **not** "significantly interfere" with IL-1ra binding. Thus, applicants have described a single antibody species that inhibits binding of **IL-1β to IL-1R1**, i.e., antibody comprising SEQ ID NOs: 16 and 18 (antibody 15C4). However, Applicants have **not** described a species with at least 90% identity to an antibody comprising SEQ ID NOs: 16 and 18, wherein said species inhibits binding of **IL-1ra to IL-1R1**.

Applicant is claiming a subgenus not supported by the specification as-filed, i.e., an antibody with at least 90% identity to an antibody comprising SEQ ID NOs: 16 and 18 wherein the antibody inhibits binding of either IL-1β ***or IL-1ra*** to IL-1R1. A generic or a sub-generic disclosure cannot support a species unless the species is specifically described.

It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Applicant's reliance on generic disclosure and a single species does not demonstrate possession of an antibody with at least 90% identity to an antibody comprising SEQ ID NOs: 16 and 18 wherein the antibody inhibits binding of either IL-1β ***or IL-1ra*** to IL-1R1.

Applicant is invited to amend the claim to "wherein the antibody inhibits binding of IL-1β to IL-1R1."

8. Claims 55 and 56 are rejected under **35 U.S.C. § 102(e)** as being anticipated by Dower et al. (U.S. Patent No. 6,511,665) as evidenced by Vigers et al. (Nature. 1997 Mar 13;386(6621):190-4).

Claims 55 and 56 were previously rejected under **35 U.S.C. § 102(e)** as anticipated by Dower et al. Applicant argues that, while Dower teaches an amino acid sequence comprising SEQ ID NO: 76 and antibodies thereto, Dower has not given any indication that antibodies which bind an amino acid sequence comprising SEQ ID NO:76 would also bind SEQ ID NO: 76, per se.

In response to applicant's assertion that Dower has not given any indication that antibodies which bind an amino acid sequence comprising SEQ ID NO:76 would also bind SEQ ID NO: 76, claims 55 and 56 are presently rejected under **35 U.S.C. § 102(e)** as being anticipated by Dower, essentially for the reasons of record set forth in the previous Office Action, as evidenced by Vigers.

Dower teaches human antibodies to the IL-1 receptor with the amino acid sequence as described in Figures 5A-C, which, as stated by applicants, encompasses SEQ ID NO: 76 of the instant application (see entire document, column 2, lines 64-66, in particular). Dower also teaches that antibodies developed against the soluble truncated form of IL-1 receptor are particularly preferred (see entire document, column 11, lines 16-17; column 5, lines 27-36 and column 27, lines 9-22, in particular). Dower further teaches that antibodies may be utilized therapeutically to block the binding of IL-1 to its receptor (see entire document, column 15, lines 7-10, in particular).

As evidenced by Vigers et al, one portion of IL-1β, "site B", which is one of two parts of IL-1β essential for interaction with IL-1R1, makes extensive contacts exclusively with domain three of soluble IL-1R1, which encompasses SEQ ID NO:76 (see entire document, particularly Results on page 191-193).

Given that Dower teaches that human antibodies developed against the soluble truncated form of IL-1 receptor are particularly preferred, and that antibodies against IL-1R1 may be utilized therapeutically to block the binding of IL-1 to its receptor, and given that antibodies which specifically recognize the extracellular domain of IL-1R1, in particular domain three of IL-1R1, would block binding of IL-1 to its receptor as evidenced by Vigers, the human antibodies of Dower, which can be used to block the IL-1 ligand to IL-1R1 receptor interaction, inherently contain antibodies that specifically bind to the polypeptide of SEQ ID NO:76.

Since the Office does not have a laboratory to test the anti-IL-1R1 antibodies of Dower, it is applicant's burden to show that the reference antibodies do not specifically bind to the polypeptide of SEQ ID NO: 76. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); *In re Fitzgerald* et al., 205 USPQ 594 (CCPA 1980).

9. No claims are allowed.

However, claim 5 is objected to because it recites SEQ ID NOs that are not part of elected Group III, and claim 10 is objected to because it depends on claim 5. Claims 5 and 10 would be allowable if the objection to claim 5 were obviated.

Moreover, claims 57 and 58 are objected to because they depend on objected claim 5 and withdrawn claims 12 and 25, which recite SEQ ID NOs not included in elected group III. Claims 57 and 58 would be allowable if the objection to claim 5 were obviated and withdrawn claims 12 and 25 were canceled.

Moreover, claim 53 is objected to because it depends on rejected claim 46. Claim 53 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
June 1, 2006

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6/5/06